T helper 17 (Th17) cells and interleukin-17A (IL-17A) produced by them are critical in autoimmune inflammatory diseases, such as psoriasis. IL-17A has been shown to signal through IL-17 receptor A/IL-17 receptor C (IL-17RA/IL-17RC) complex to drive inflammatory responses. However, in a psoriasis model, we found that IL17rc deficiency did not completely ameliorate the disease, suggesting another receptor. In search for another IL-17A–interacting receptor, we found that IL-17D directly bound IL-17A but not IL-17F or IL-17A/F heterodimer and formed a heterodimer with IL-17RA. IL-17A–, but not IL-17F– or IL-17A/F–, mediated gene expression was defective in IL17rd-deficient keratinocytes. IL17rd deficiency in nonhemopoietic cells attenuated imiquimod-induced psoriasis-like skin inflammation. Although IL-17RC and IL-17RD differentially activated IL-17A–dependent signaling and gene expression, their compound mutation led to complete deficits in keratinocytes. IL-23 was found induced by IL-17A in keratinocytes, dependent on both IL-17RC and IL-17RD, suggesting feed-forward regulation of IL-17/IL-17 axis in psoriasis. Together, IL-17RD constitutes a second functional receptor for IL-17A and, together with IL-17RC, mediates the proinflammatory gene expression downstream of IL-17A.
RESULTS

**Il17rc deficiency does not completely abolish IMQ-induced psoriasis-like skin inflammation**

Although targeting IL-17A or IL-17RA is effective in treating psoriasis, the role of IL-17RC in IL-17A–mediated diseases has not been explored. Here, we generated the Il17rc knockout (KO) mice with a 44–base pair deletion in the exon 5 by CRISPR-cas9 technology to examine its role in IL-17A–driven inflammation. Il17rc KO mice were born normally and completely deficient in IL-17RC expression (fig. S1A). The IMQ-induced psoriasis-like skin inflammation was induced in Il17rc-deficient (Il17rc−/−) mice along with age-matched wild-type (WT) and Il17a/f DKO controls. Upon IMQ treatment for 5 days, WT mice developed typical psoriasis-like skin inflammation that was nearly absent in Il17a/f DKO mice (Fig. 1A). However, Il17rc KO mice still developed partial skin inflammatory disorders, including intermediate levels of epidermal thickness (Fig. 1A) and dermal infiltration of neutrophils (Fig. 1, B and C) and γδ T cells (Fig. 1D), compared with WT and Il17a/f DKO mice. In line with this, the expression of psoriasis-related genes including Cxcl1, Cxcl20 and Cxcl5, S100a8, and S100a9, and the adhesion molecule Icam1 was significantly reduced in Il17rc KO mice when compared with the WT mice but noticeably higher than in Il17a/f DKO mice (Fig. 1E). Together, these results suggest that IL-17A may signal through an alternative receptor other than the IL-17RA/IL-17RC complex in IMQ-induced psoriasis-like skin inflammation.

**IL-17RD functions as a receptor for IL-17A in mouse keratinocytes**

To determine whether IL-17A could signal through alternative receptor(s), we tested the interaction of mouse IL-17A (mIL-17A) with the murine IL-17RA, IL-17RC, and IL-17RD overexpressed in 293T cells. mIL-17A could also bind mIL-17RD, in addition to mIL-17RA and mIL-17RC. As a contrast, none of other IL-17 family cytokines showed significant binding to mIL-17RD (Fig. 2A and fig. S2, A and B).

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![Fig. 1. Il17rc deficiency is insufficient to completely abolish IMQ-induced psoriasis-like skin inflammation.](http://immunology.sciencemag.org/)

WT, Il17a and Il17T DKO, and Il17rc KO mice (n = 10) were subjected to IMQ-induced psoriasis-like skin inflammation and euthanized together with the untreated WT mice 5 days after disease induction. (A) Representative H&E staining of skin sections (10×) and statistical data. (B to D) The frequencies of leukocytes (B), neutrophils (C), and γδ T cells (D) in dermis. (E) The relative mRNA level of selected genes from the total skin. The results were repeated three times with consistent results. Data were shown as means ± SEM. P values were determined by unpaired t test or one-way ANOVA, followed by Tukey’s post hoc test. *P < 0.05 compared with indicated group.
Fig. 2. mIL-17RD binds to mIL-17A and forms a heterodimer with mIL-17RA. (A) The binding of His-tagged IL-17 family cytokines (IL-17A to IL-17F) to IL-17RD–expressing 293T cells. (B) The interaction between IL-17A/IL-17RD and IL-17-RD/IL-17RD detected by BiFC. (C) The binding of IL-17A to IL-17RA/IL-17RD or IL-17-RD/IL-17RD–expressing 293T cells. FITC, fluorescein isothiocyanate. (D) The binding of IL-17 family cytokines to IL-17RA/IL-17RD or IL-17-RD/IL-17RD dimer. (E) The interaction between IL-17RA/IL-17RD and IL-17-RD/IL-17RD detected by immunoprecipitation. IP, immunoprecipitation; IB, immunoblot. (F) The interaction between mIL-17RA and mIL-17RD in mouse primary keratinocytes. (G) The colocalization of mIL-17RA and mIL-17RD in primary mouse keratinocytes. (H) Relative mRNA levels of selected genes from primary mouse keratinocytes stimulated with different cytokines (means ± SEM). All results were repeated three times with consistent results. P values were determined by unpaired t test. *P < 0.05 compared with indicated group.
In addition, in the bimolecular fluorescence complementation (BiFC), we overexpressed mIL-17RA, mIL-17RC, and/or mIL-17RD as fusion proteins with yellow fluorescent protein (YFP) N-terminal (YFP-N) or YFP C-terminal (YFP-C) in 293T cells, respectively, and found that the yellow fluorescent signals were clearly detected in cells coexpressing YFP-N and YFP-C, but not in cells coexpressing YFP-N and YFP-C. This suggests interactions between mIL-17RA and mIL-17RD or mIL-17RD homotypic interactions (Fig. 2B). mIL-17A preferentially bound to YFP high cells expressing mIL-17RA/mIL-17RD or mIL-17RD/mIL-17RD dimers (Fig. 2C), which was not observed for other IL-17 family cytokines, including mIL-17F (Fig. 2D). Moreover, hemagglutinin (HA)-tagged mIL-17RA or mIL-17RD, but not mIL-17RC, could be communoprecipitated by an antibody against Flag-tagged mIL-17RD in 293T cells (Fig. 2E), suggesting the presence of mIL-17RA/mIL-17RD and mIL-17RD/mIL-17RD dimeric complexes in the overexpression system, further supporting IL-17RD as a potential receptor for IL-17A.

To test the receptor interaction under physiological conditions, we assessed the binding of mIL-17RD with mIL-17RA in primary keratinocytes. mIL-17RD could be readily communoprecipitated with mIL-17RA with or without mIL-17A treatment, suggesting that the mIL-17RA/mIL-17RD heterodimer formation was ligand independent (Fig. 2F). The result was further confirmed by colocalization of mIL-17RA and mIL-17RD in mouse primary keratinocytes according to confocal microscopy assays (Fig. 2G). In addition, using cross-linking and communoprecipitation methods, we found mIL-17RA/mIL-17RD heterodimers but not mIL-17RD/mIL-17RD homodimers as the predominant form of IL-17RD-containing receptor complex in primary mouse keratinocytes (Fig. S2C).

To assess whether mIL-17RD could functionally regulate IL-17A signaling, WT or Il17rd KO primary mouse keratinocytes were stimulated with mIL-17A, mIL-17C, or mIL-25 and then were evaluated for psoriasis-related proinflammatory gene expressions. mIL-17A–induced Cxcl1, Cxcl2, S100a9, and Ccl20 expression was inhibited by the absence of Il17rd, whereas IL-17C– or IL-25–dependent gene expression was not affected, suggesting a selective role for IL-17RD in mediating IL-17A downstream signaling (Fig. 2H and fig. S2D).

### IL-17RD functions as a receptor for IL-17A in human keratinocytes

To validate the human relevance of our data, we overexpressed human IL-17RD (hIL-17RD) in 293T cells. Similar to the findings in mouse system, hIL-17A bound hIL-17RD (Fig. 3A), which could also be readily communoprecipitated with hIL-17RA in both HaCaT cells and primary human keratinocytes and colocalize with hIL-17RA (Fig. 3, B to D) even without hIL-17A stimulation (Fig. 3C), again suggesting a ligand-independent interaction between hIL-17RA and hIL-17RD (Fig. 3C).

To examine whether IL-17RD is also involved in hIL-17A signaling, the human IL17RD expression was knocked down in primary human keratinocytes by short hairpin–mediated RNA (shRNA) lentivirus and the knockdown efficiency was tested by Western blot (fig. S1, B and C). Similar to the mouse results, hIL-17A–induced gene expression was also reduced by IL17RD knockdown (Fig. 3E), including CXCL1, CXCL2, CCL20, and S100A8, known to be involved in the pathological progress of psoriasis, suggesting a conserved role of IL-17RD between human and mouse.

### IL-17RD is required for IMQ-induced psoriasis-like skin inflammation

To understand the in vivo role of IL-17RD, we subjected the Il17rd−/− mice to IMQ-induced skin inflammations. Similar to Il17rc KO mice, IMQ-induced pathological changes were decreased but still obvious in Il17rd KO mice compared with WT mice and untreated controls (Fig. 4A and fig. S3A). Neutrophils and γδ T cells were both reduced in the lesional skin of Il17rd KO versus WT mice (Fig. 4, B to D), suggesting a decreased in situ inflammatory response in the KO mice. However, no difference in skin ILC3s was detected (Fig. 4E). In the skin-draining lymph node (dLN), Il17rd KO mice showed slightly increased γδ T population, whereas the CD4+ T cell frequency remained largely normal (fig. S3B).

We also analyzed the mRNA expression of proinflammatory chemokines and cytokines in the total skin tissue from Il17rd KO or WT mice after IMQ treatment. The expression of Cxcl1 and Ccl20, two chemokines responsible for the recruitment of neutrophils and lymphocytes, was reduced (Fig. 4F), as well as the antimicrobial peptides S100a8 and S100a9, chemokine Cxcl5, and adhesion molecule Icam1 (Fig. 4F). Noticeably, the phenotypes of Il17rd KO, characterized by diminished acanthosis, skin infiltration of leukocytes, and the expression of psoriasis-related genes, appeared weaker than that in Il17rc KO (fig. S3A).

To further assess the function of IL-17RD, we adopted a chronic IMQ application model (23), in which IMQ was painted on the ears of mice for 15 days. Consist with the short-term model, Il17rd KO significantly reduced the ear inflammation as judged by thickness in Il17rd KO mice compared with WT mice (fig. S3C). Together, these results suggest an important and necessary role of IL-17RD in IL-17A–dependent skin inflammatory response.

### IL-17RD expression in keratinocytes is important for psoriasis-like skin inflammation in vivo

To understand the mechanisms whereby IL-17RD functions in IMQ-induced psoriasis-like skin inflammation, we examined the expression of IL-17RD in different cell compartments in the skin. The Il17rd mRNA was barely detected in skin-derived leukocytes but was highly expressed in keratinocytes in healthy mice (Fig. 5A), specifically the full-length isoform (GenBank accession no. BC138629.1) but not the short version reported by Rong et al. (24) (GenBank accession no. AF492091.1). In the IMQ-induced psoriasis-like skin inflammation, IMQ treatment up-regulated Il17rd transcript in CD45− but not in CD45+ cells (Fig. 5A). Consistently, IL-17RD protein was expressed by nearly all nucleated cells in epidermis (including stratum basale and stratified squamous epithelia), which are largely composed of keratinocytes, and further increased after IMQ treatment as determined by immunofluorescence (fig. S4A).

To further determine the source and function of IL-17RD, we established IMQ-induced psoriasis-like skin inflammation model using Il17rd−/− bone marrow chimeric mice (fig. S4B). As a result, IL-17RD deficiency in nonhematopoietic cells (WT to KO and KO to KO mice) exhibited decreased psoriasis-like skin inflammations compared with the WT chimeric mice receiving WT or Il17rd KO bone marrow, characterized by diminished skin infiltration of total leukocytes and neutrophils (Fig. 5B). Consistent with germline KO mice, γδ T cells, but not ILC3s, were significantly reduced in the lesional skin of chimeric mice with nonhematopoietic depletion of IL-17RD (WT to KO and KO to KO mice) versus the WT chimeric mice.
In skin dLNs, mice lacking IL-17RD in nonhematopoietic cells (WT to KO and KO to KO) were observed with slightly increased \( \gamma \delta \) T frequencies as compared with WT to WT and KO to WT mice, whereas the frequencies of CD4\(^+\) T cells were comparable between groups (fig. S4C). In line with this, the expression of psoriasis-related proinflammatory genes was also reduced in the chimeric mice with nonhematopoietic depletion of IL-17RD (Fig. 5E). Considering that \( \text{Il17rd} \) deficiency significantly reduced

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**Fig. 3. hIL-17RD binds to hIL-17A and forms a heterodimer with hIL-17RA.**

(A) The binding of biotin-labeled hIL-17 to hIL-17RD–expressing 293T cells. (B) The interaction between hIL-17RA and hIL-17RD in human keratinocytes cell line (HaCaT) after hIL-17A stimulation. (C) The interaction between hIL-17RA and hIL-17RD in primary human keratinocytes. (D) The colocalization of hIL-17RA and hIL-17RD in primary mouse keratinocytes. (E) The relative mRNA level of selected genes from WT or IL17RD knockdown (KD) primary human keratinocytes stimulated with hIL-17A (means ± SEM). (F) The mRNA level of IL-17RC and IL-17RD in patients with psoriasis (means ± SEM). GAPDH, glyceraldehyde-3-phosphate dehydrogenase. (A to F) All results were repeated three times with consistent results. P values were determined by unpaired \( t \) test. (A to G) \( P < 0.05 \) compared with indicated group and \( **** P < 0.0001 \) compared with normal patients.
IL-17–induced proinflammatory gene expression in keratinocytes, these data together point an essential role of keratinocyte-derived IL-17RD in IL-17A–dependent skin inflammations.

In contrast to the findings in murine models, the IL-17 family receptors, particularly those cytokine-specific receptors, including IL-17RC (for IL-17A), IL-17RE (for IL-17C), and IL-17RB (for IL-25), as well as IL-17RD, were all greatly decreased compared with healthy controls, and only the common receptor, IL-17RA, was increased in human patients with psoriasis (25), which was also confirmed by our studies (Fig. 3, F and G). It is possible that reduced expression of IL-17RD and IL-17RC might be caused by negative feedback regulation of persistent IL-17A signaling during chronic inflammation, whereas the low but not zero expression level of these receptors is still functional.

**Il17rd deficiency has a global effect on IL-17A–mediated gene expression in keratinocytes**

To understand the overall function of IL-17RD in IL-17A signaling, we performed RNA sequencing (RNA-seq) with WT and Il17rd KO primary mouse keratinocytes after IL-17A treatment (Il17rd differentially expressed genes listed in data file S1) along with untreated WT control. In total, IL-17A up-regulated 1170 genes, among which 315 (26.9%) were reduced in Il17rd KO keratinocytes, whereas only 11 were further up-regulated as a result of Il17rd deficiency (>2-fold change, P < 0.05). IL-17A inhibited 1296 genes, among which 689 genes were up-regulated and 8 were down-regulated because of Il17rd deficiency (>2-fold change, P < 0.05). This result firmly supports IL-17RD as a functional receptor for IL-17A.

To further understand the function of IL-17RD, we performed KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis. Among the top 15 IL-17A up-regulated pathways (P < 0.001), many were associated with cell proliferation (cell cycle, DNA replication) and proinflammatory signaling (IL-17 signaling pathway, cytokine-cytokine receptor interaction, and TNF signaling pathway) and eight were dependent on IL-17RD, including IL-17 signaling pathway, TNF signaling pathway, and cytokine-cytokine receptor interaction. Despite the highly consistent gene regulatory patterns, Il17rd deficiency did not reduce IL-17A–dependent gene expression to basal levels as in unstimulated cells (Fig. 6C), again supporting IL-17RD as an important, yet not sole, receptor for IL-17A in keratinocytes.

**Both IL-17RC and IL-17RD regulate IL-17A signaling in keratinocytes**

Our above study showed that IL-17RC and IL-17RD were mutually important in IL-17–dependent psoriasis-like skin inflammatory response. To understand the basis for their differential functions, we determine their binding affinity with mIL-17A by saturation binding studies using purified mIL-17RC–hIg or mIL-17RD–hIg fusion
proteins. IL-17A bound to IL-17RD with an affinity roughly 20-fold less than to IL-17RC, with median effective concentration (EC50) of 2.57 and 0.126 nM, respectively (Fig. 7A), which may account for the relatively weaker phenotypes in Il17rd KO than Il17rc KO mice in the IMQ-induced psoriasis-like skin inflammation model.

**Fig. 5.** IL17rd deficiency in nonhemopoietic cells causes resistance to IMQ-induced psoriasis-like skin inflammation. (A) IL-17RD expression in the skin tissue of WT mice (n = 4). Left: Relative mRNA level of Il17rd in total skin, and different types of cells from the skin at steady state. N/A, not applicable. Right: Relative mRNA level of Il17rd from the total skin, CD45− cells and CD45+ cells of the skin of WT mice treated with or without IMQ for 5 days (n = 5). *P < 0.05 compared with total skin and #P < 0.05 compared with indicated group. (B to D) The frequencies of leukocytes [(B), top], neutrophils [(B), bottom], γδ T cells (C), and ILC3s (D) in the dermis of chimeric mice (n = 6). n.s., not significant. (E) The relative mRNA level of selected genes from the total skin of chimeric mice. The results were repeated three times with consistent results. Data were shown as means ± SEM. P values were determined by unpaired t test or one-way ANOVA, followed by Tukey’s post hoc test. *P < 0.05 compared with indicated group.
In line with above studies, Il17rc/Il17rd DKO keratinocytes were completely defective in IL-17A–induced activation of NF-κB, p38 mitogen-activated protein kinases (p38), extracellular signal–regulated kinases (ERK), and c-Jun N-terminal kinase (JNK) pathways, whereas Il17rc KO keratinocytes showed decreased NF-κB activation and abolished p38 and ERK and JNK phosphorylation in response to IL-17A (Fig. 7B and fig. S6). As a comparison, Il17rd deficiency led to a relatively milder defect in NF-κB and ERK signaling but abolished p38 and JNK activation after IL-17A treatment (Fig. 7B).

To further understand the distinct and redundant functions of IL-17RC and IL-17RD in IL-17A signaling, we conducted the RNA-seq analysis on IL-17A–stimulated WT, Il17rc KO primary mouse keratinocytes and compared (Fig. 7C). Together, Il17rc and Il17rd deficiency led to dysregulated expression of 1813 genes when compared with WT keratinocytes after IL-17A stimulation (>2-fold change, q < 0.05). The 1813 differentially expressed genes were split into six different clusters by K-means clustering: cluster 1, up-regulated in both Il17rc and Il17rd KO; cluster 2, down-regulated in both Il17rc and Il17rd KO; cluster 3, up-regulated only in Il17rc KO; cluster 4, up-regulated only in Il17rd KO; cluster 5, down-regulated only in Il17rc KO; and cluster 6, down-regulated only in Il17rd KO. The KEGG pathway analysis was performed on differentially expressed genes in each cluster, and the top enriched pathways of each cluster were identified (Fig. 7C). Specifically, the differentially expressed genes down-regulated in both Il17rc and Il17rd KO (cluster 2) were mainly associated with cytokine-cytokine receptor interaction and IL-17A signaling pathway, suggesting overlapping functions of IL-17RC and IL-17RD in mediating IL-17A signaling. Genes in cluster 5 (unique genes positively regulated by IL-17RC) were specifically associated with mitogen-activated protein kinase signaling pathway, and genes in cluster 6 (unique genes positively regulated by IL-17RD) were related to cholesterol metabolism, suggesting unique functions of IL-17RC and IL-17RD besides their common role in regulating IL-17A signaling.

The Venn diagram was used to analyze the numbers of overlapped differentially expressed genes (comparing with IL-17A–treated WT) in Il17rc KO up-regulated, Il17rc KO down-regulated, Il17rd KO up-regulated, and Il17rd KO down-regulated groups (Fig. 7D). More than 50% of genes were overlapped between the two KOs, suggesting that most of the genes were commonly regulated by both IL-17RC and IL-17RD. Noticeably, most of the overlapped genes were either commonly up-regulated (524 genes) or down-regulated (254 genes) in both Il17rc and Il17rd KO cells. We found that only 16 genes were up-regulated in one KO but down-regulated in the other. This result strongly indicates the overlapping functions of IL-17RC and IL-17RD.

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**Fig. 6.** Il17rd deficiency reduces IL-17A downstream gene expression. (A) The percentages of IL-17RD–related genes among all IL-17A regulated genes. (B) KEGG pathway analysis of IL-17RD–related pathways (marked by “*”) among IL-17A up- and down-regulated pathways. (C) Verify the mRNA level of selected genes from WT and Il17rd KO primary mouse keratinocytes by qPCR (means ± SEM). PPAR, peroxisome proliferator–activated receptor; AGE-RAGE, advanced glycation end-products and their receptor. P values were determined by one-way ANOVA, followed by Tukey’s post hoc test. #P < 0.05 compared with untreated WT and *P < 0.05 compared with IL-17A–treated WT.
Fig. 7. IL-17RC and IL-17RD differentially regulates IL-17A downstream events in keratinocytes. (A) The saturation binding of IL-17RC–ecd and IL-17RD–ecd to IL-17A (means ± SEM). CBS, citrate-buffered saline; OD, optical density. (B) Phosphorylation of p38, IkBα, Erk, and JNK in primary mouse keratinocytes cultured with IL-17A for different time points. Results shown are representative data of three independent experiments. (C) Heatmap of normalized RPKM data from WT, Il17rc KO, and Il17rd KO keratinocytes treated with IL-17A. The top enriched pathways of each cluster were listed aside. HTLV-I, human T cell leukemia virus I. (D) Venn diagram showing the numbers and overlap of the differentially expressed genes (comparing to IL-17A–treated WT) among the four comparisons. (E) The pathways that are commonly down-regulated by Il17rc and Il17rd KO.
The KEGG pathway analysis was performed on the differentially expressed genes (254 genes) commonly down-regulated in both $\text{Il}17rc$ and $\text{Il}17rd$ KO cells. As a result, the top 10 pathways were mainly associated with proinflammatory functions, including IL-17A signaling pathway, TNF signaling pathway, chemokine signaling pathway, and cytokine-cytokine receptor interaction pathways (Fig. 7E). We further verified the expression of some genes closely related to psoriasis development by real-time quantitative polymerase chain reaction (RT-qPCR). The expression of $\text{Il}23a$, $\text{Cxcl}1$, $\text{Ccl}20$, and $\text{Ccl}20$ was affected by both $\text{Il}17rc$ and $\text{Il}17rd$ deficiency (figs. S6 and S7). However, the expression of IL-1 family cytokines $\text{Il}1f6$ and $\text{Il}1f8$ was uniquely regulated by IL-17RC. Meanwhile, IL-17RD seemed to be more important for the expression of psoriasis-related epidermal response genes $\text{Tgfa}$ and $\text{Csf}3$ (fig. S6). In addition, we also tested the roles of IL-17RC and IL-17RD in regulating IL-17A/F or IL-17F signaling. IL-17A/F– and IL-17F–mediated gene expression were defective only in $\text{Il}17rc$ but not $\text{Il}17rd$ KO keratinocytes (fig. S8, A and B), indicating that IL-17RD is selectively required for IL-17A but not for IL-17A/F or IL-17F signaling.

**IL-17A regulates IL-23 expression in keratinocytes**

Myeloid cells are generally regarded as the major source of IL-23 in inflammatory response. However, IL-23 can be also expressed by keratinocytes in human patients with psoriasis (26) and is important for chronic skin inflammation in a mouse model of psoriasis (27). In this study, we found that IL-17A directly induced the mRNA expression of $\text{Il}23a$ and $\text{Il}12b$ that encode the two IL-23 subunits (Fig. 8A), and the protein level of IL-23 in keratinocytes (fig. S9A), dependent on both IL-17RC and IL-17RD. In contrast, the IL-12–specific subunit $\text{Il}12a$ was not increased (Fig. 8A). On the other hand, IL-1α, IL-1β, and TNF-α could not induce or further increase IL-23 expression, either alone or in combination with IL-17A. These data together suggest a specific and selective role of IL-17A in inducing IL-23 expression (Fig. 8B). Consistently, IL-17A–induced $\text{Il}23a$ expression was $\text{Act}1$ dependent and could be blocked by the NF-κB or ERK inhibitors (fig. S9, B and C).

In the IMQ-induced psoriasis-like skin inflammation model, IL-23 expression was observed in both the epidermis and the dermis in the WT mice based on immunofluorescence staining (Fig. 8C). However, the expression of IL-23 in epidermis was significantly reduced in $\text{Il}17rd$ KO or $\text{Il}17rc$ KO mice and was nearly absent in the $\text{Il}17a/f/DKO$ mice (Fig. 8C), again supporting a critical and selective role of IL-17A in regulating keratinocyte-derived IL-23 under in vivo settings.

In the IMQ-induced psoriasis-like skin inflammation model, IL-23 was thought to be mainly derived from dermal DCs and macrophages (11). To explore the functional importance of IL-23 expressed by keratinocytes, we established an IMQ-induced psoriasis-like skin inflammation model using $\text{Il}23a$ KO bone marrow chimeric mice. We found that the chimeric mice receiving WT bone marrow had more severe psoriasis than those receiving KO WT bone marrow, characterized by severe acanthosis (Fig. 8D), increased frequencies of dermal infiltrating CD45+ cells (fig. S10A) and γδ T cells (Fig. 8E), and elevated $\text{Il}23a$ mRNA expression (Fig. 8F), suggesting that hematopoietic cell–derived IL-23 was indeed important for psoriasis progression. Significant differences were also observed between WT and KO recipient mice receiving WT bone marrows in terms of γδ T cell frequency and $\text{Il}23a$ mRNA level (Fig. 8, E and F), suggesting that radio-resistant cell-derived IL-23 is also important in the development of complete psoriasis-like skin inflammation.

To examine whether IL-17RD also regulates IL-23 production in different cell types, we isolated various types of cells from the IMQ-treated WT and $\text{Il}17rd$ KO mice and analyzed them for IL23 expression. $\text{Il}17rd$ deficiency did not affect the transcription of $\text{Il}23a$ in Langerhans cells, dermal DCs, and macrophages or their numbers (Fig. 8, G and H). In contrast, $\text{Il}17rd$ deficiency not only reduced the level of keratinocyte-derived IL-23 but also the number of keratinocytes (Fig. 8, G and H), possibly because of diminished acanthosis in $\text{Il}17rd$ mice. Consistent with the immunofluorescence staining data, $\text{Il}17rd$ deficiency caused an overall reduction of $\text{Il}23a$ mRNA expression in the total lesional skin (Fig. 8I). These data together suggest that $\text{Il}17rd$–dependent IL-23 expression in nonhematopoietic cells, specifically keratinocytes, represents a significant source of IL-23 in skin inflammations.

In line with the role of IL-23, $\text{Il}17rd$ deficiency reduced the frequencies of IL-17+ γδ T and ILC3 cells compared with WT control mice (fig. S10B), as well as $\text{Il}17a$ mRNA level in the lesional skin (fig. S10C), but did not affect $\text{Il}17c$, $\text{Il}25$, and $\text{Il}17f$ expressions (fig. S10C). Our findings thus demonstrate an IL-17A–dependent expression of IL-23 in keratinocytes, which could serve as an additional positive feed-forward loop in sustaining the well-known IL-23 → IL-17 axis in psoriasis-like skin inflammation.

**DISCUSSION**

In this study, we identified the orphan receptor IL-17RD as a functional receptor for IL-17A. In the IMQ-induced psoriasis-like skin inflammation, IL-17A signals through both IL-17RC and IL-17RD to activate downstream proinflammatory gene expression, and deficiency in either IL-17RC or IL-17RD resulted in partially defective IL-17A signaling in keratinocytes and partial resistance to the IMQ-induced psoriasis-like skin inflammation, whereas deficiency in both IL-17RC and IL-17RD caused complete loss of IL-17A signaling.

To date, the IL-17RA/IL-17RC complex has been widely known as the only receptor for IL-17A, IL-17F, and IL-17A/F heterodimer (28, 29). Recent studies suggest that IL-17RD could affect IL-17A signaling or gene expressions in MEFs according to reporter assays (20) and in bone marrow–derived macrophages and U373 cells through shRNA knockdown experiments (19). It is also reported that IL-17RD could interact with IL-17RA in MEFs and NIH3T3 cells and with TRAF6, an adaptor protein essential for IL-17 signaling, under overexpression system (20). Despite these findings, IL-17RD has not been proposed as an alternative receptor for IL-17A due to lack of evidences of direct interaction between IL-17A and IL-17RD (20). This study provides strong support for the role of IL-17RD in regulating IL-17A signaling and may have implications for the development of IL-17RD antagonist-based therapeutics for psoriasis.

2. Myeloid cells are generally regarded as the major source of IL-23 in inflammatory response. However, IL-23 can be also expressed by keratinocytes in human patients with psoriasis (26) and is important for chronic skin inflammation in a mouse model of psoriasis (27). In this study, we found that IL-17A directly induced the mRNA expression of $\text{Il}23a$ and $\text{Il}12b$ that encode the two IL-23 subunits (Fig. 8A), and the protein level of IL-23 in keratinocytes (fig. S9A), dependent on both IL-17RC and IL-17RD. In contrast, the IL-12–specific subunit $\text{Il}12a$ was not increased (Fig. 8A). On the other hand, IL-1α, IL-1β, and TNF-α could not induce or further increase IL-23 expression, either alone or in combination with IL-17A. These data together suggest a specific and selective role of IL-17A in inducing IL-23 expression (Fig. 8B). Consistently, IL-17A–induced $\text{Il}23a$ expression was $\text{Act}1$ dependent and could be blocked by the NF-κB or ERK inhibitors (fig. S9, B and C).

In the IMQ-induced psoriasis-like skin inflammation model, IL-23 expression was observed in both the epidermis and the dermis in the WT mice based on immunofluorescence staining (Fig. 8C). However, the expression of IL-23 in epidermis was significantly reduced in $\text{Il}17rd$ KO or $\text{Il}17rc$ KO mice and was nearly absent in the $\text{Il}17a/f/DKO$ mice (Fig. 8C), again supporting a critical and selective role of IL-17A in regulating keratinocyte-derived IL-23 under in vivo settings.

In the IMQ-induced psoriasis-like skin inflammation model, IL-23 was thought to be mainly derived from dermal DCs and macrophages (11). To explore the functional importance of IL-23 expressed by keratinocytes, we established an IMQ-induced psoriasis-like skin inflammation model using $\text{Il}23a$ KO bone marrow chimeric mice. We found that the chimeric mice receiving WT bone marrow had more severe psoriasis than those receiving KO WT bone marrow, characterized by severe acanthosis (Fig. 8D), increased frequencies of dermal infiltrating CD45+ cells (fig. S10A) and γδ T cells (Fig. 8E), and elevated $\text{Il}23a$ mRNA expression (Fig. 8F), suggesting that hematopoietic cell–derived IL-23 was indeed important for psoriasis progression. Significant differences were also observed between WT and KO recipient mice receiving WT bone marrows in terms of γδ T cell frequency and $\text{Il}23a$ mRNA level (Fig. 8, E and F), suggesting that radio-resistant cell-derived IL-23 is also important in the development of complete psoriasis-like skin inflammation.
on IL-17A–inhibited gene expression, among which 53.1% (689 versus 1296 genes) were dependent on IL-17RD. Consistent with these findings, Il17rd deficiency partially ameliorated IMQ-induced IL-17A–dependent psoriasis-like skin inflammation. Thus, our molecular, cellular, and functional studies together established IL-17RD as a functional receptor for IL-17A, at least in keratinocytes.

In this study, we also did a side-by-side comparison between IL-17RC and IL-17RD in their function and signaling. In contrast to IL-17RC, our data show that IL-17RD exclusively binds IL-17A, but not IL-17F or IL-17A/F, and that Il17rd deficiency does not affect IL-17F– or IL-17A/F–mediated gene expression. IL-17F is also indicated in the pathogenesis of psoriasis (30), which may be one of
the reasons why the phenotypes of Il17rc deficiency were stronger than Il17rd deficiency in IMQ-induced psoriasis-like skin inflammation. Another reason could be caused by its weaker binding affinity with IL-17A than IL-17RC (~20-fold less), which is also reflected by the fact that Il17rc deficiency largely abolished IL-17A–induced activation of p38, JNK, NF-κB, and ERK signaling in keratinocytes, whereas Il17rd deficiency mainly impaired p38 and JNK activation but barely affected NF-κB and ERK signaling pathways. The identification of IL-17RD as a selective receptor for IL-17A could be useful in developing more specific therapeutic strategies against IL-17A–dependent inflammatory diseases, although its function in tissues other than skin needs further elucidation. Transcriptome analysis suggests that the functions of IL-17RC and IL-17RD were largely overlapped, particularly in regulating genes involved in proinflammatory responses. It is unclear why both receptors are required in the same cell type for IL-17A signaling. Considering the overlapping functions between IL-17RC and IL-17RD, it is possible that one receptor could compensate for the loss of the other receptor and may even enhance certain aspects of IL-17A signaling under certain conditions, which may explain the controversial results in the literature on IL-17RD functions. Among the few uniquely regulated genes, IL-17RC specifically regulates cell cycle–related genes, whereas IL-17RD selectively regulates cholesterol metabolism–related genes. It has been reported that cholesterol depletion significantly reduced the expression of IL-17A–induced Ccl20, Il8, and S100a7 expression in keratinocytes, which was also dependent on IL-17RD.

The IL-23/IL-17 axis has been identified as the major pathogenic driver in development of psoriasis (7, 11). Consistent with a recent study that keratinocyte–derived IL-23 is important in the pathogenesis of psoriasis (27), our study showed that nonhematopoietic cell–derived IL-23 constituted a significant portion of total skin IL-23 pool and was required for the full development of psoriasis-like skin inflammation. Moreover, our studies find that IL-17A could directly stimulate IL-23 expression in keratinocyte via both the IL-17RC and IL-17RD receptors. Previous studies have shown DCs and macrophages as an important source role of IL-23 in psoriasis-like skin inflammation, which was also confirmed in our mix bone marrow chimera studies. It is possible that the hematopoietic source of IL-23 plays a crucial role in initiating the differentiation or activation of IL-17A–producing cells, whereas the local keratinocyte–derived IL-23 is important in sustaining the IL-23/IL-17 axis in chronic skin inflammatory diseases.

In summary, our work has demonstrated IL-17RD as a functional receptor for IL-17A in vitro and in vivo. Although its role in other IL-17A–related inflammation need to be further explored, our study reveals the complexity of receptor/ligand interaction in the IL-17 family. Further investigation might benefit developing more specific targeting strategy in treatment of IL-17–related immune diseases.

MATERIALS AND METHODS

Study design

The objective of this study was to explore the role of the orphan receptor IL-17RD in psoriasis-like skin inflammation. The sample size (n = 10) was determined by power analysis (power, 0.83), the sex of the mice (female only) was determined according to previous studies, and the endpoint (5 days) was determined according to our own kinetic studies. The mice were randomly assigned to different groups, and repeat experiments were carried out by two to three times. The investigators were not blinded when conducting or analyzing the experiments, and no data were excluded.

Mice

Il17rd−/− (31) and Il23a−/− mice were obtained from the Mutant Mouse Regional Resource Center (National Institutes of Health). Il17rc−/− mice were generated by CRISPR-Cas9 as described (see the Supplementary Materials) (32). Il17a (29) and Il17f DKO (Il17a−/−Il17f−/−) mice (see the Supplementary Materials) were produced in our laboratory. Mice used in this study were all on C57BL/6 background and housed in the specific pathogen–free animal facility at Tsinghua University. Protocols of animal experiments were approved by the Institutional Animal Care and Use Committee at Tsinghua University.

Psoriasis mouse model

IMQ-induced psoriasis-like skin inflammation was induced in 6- to 8-week-old mice (C57BL/6 background) by a daily topical dose of 62.5 mg of IMQ cream (5%) (Aladara, 3 M Pharmaceuticals) on the shaved back skin for five consecutive days (11). For chronic IMQ application model, 6- to 8-week-old mice (C57BL/6 background) were treated with 10 mg of IMQ cream on the ear for 15 days. The ear thickness was measured daily. The mice were then euthanized at day 16 for histology analysis [hematoxylin and eosin (H&E) staining].

Skin cell preparation and flow cytometry

Skin cells were prepared according to previous studies with minor modifications (11). Briefly, the epidermis and dermis were separated using dispase [25 U/ml in phosphate-buffered saline (PBS); 37°C for 90 min]. For keratinocytes sorting, the epidermis was further digested by 0.05% trypsin (37°C for 15 min). For flow cytometry analysis, the epidermis was discarded, and the dermal cells were separated by collagenase and hyaluronidase digestion [10 mM Heps, collagenase IV (300 U/ml), hyaluronidase (100 U/ml), and deoxyribonuclease (200 U/ml) in Dulbecco’s modified Eagle’s medium (DMEM); 37°C, 45 min]. For intracellular IL-17 staining, cells were stained with phorbol 12-myristate 13-acetate/ionomycin for 4 hours in the presence of GolgiPlug (BD Biosciences). Isolated cells were first stained with different cell surface markers [CD45 for leukocytes; CD45+Gr-1−, and CD11b+ for neutrophils; CD45−, CD3+, and γδ T cell receptor (TCRγδ) for γδ T cells; CD45+, CD3+, and CD90+ for ILC3; CD45+, major histocompatibility complex II (MHCII+), and langerin+ for Langerhans cells; CD45+ and CD49f+ for keratinocytes; CD11c+ and MHCII+ for DCs; and CD11b+, Ly6C+, and F4/80+ for macrophages]. The cells were then fixed, permeabilized, and used for intracellular staining of IL-17 or retinoic acid receptor–related orphan nuclear receptor γ (RORγt) (for ILC3). The relevant isotype control mAbs were also used. Samples were analyzed using Fortessa (BD Biosciences) and FlowJo software (TreeStar).

Histology and immunofluorescence staining

Formalin-fixed, paraffin-embedded tissue sections (~5 μm in thickness) mounted on glass slides were used for histology studies. The H&E staining was performed as previously described (33). The thickness of epidermis was calculated on the basis of the total area versus the length of epidermis or dermis, as previously described (23, 34). For immunofluorescence, frozen sections of mouse skin were stained with antimouse IL-23 (BioLegend) or antimouse IL-17RD (Abcam) primary antibody, followed by Alexa Fluor 488–conjugated
Secondary antibody. The fluorescence image was taken with confocal microscope (Nikon) and analyzed by ImageJ software.

**Primary keratinocyte culture and analysis**

The primary epidermal keratinocytes were separated from neonatal C57BL/6 mice using dispase (25 U/ml in PBS) digestion overnight at 4°C, followed by 10 min (0.05%) trypsin-EDTA digestion at 37°C (11). The primary keratinocytes were cultured with 154CF medium and Human Keratinocyte Growth Supplement (HKGS) kit (Invitrogen) and stimulated with different cytokines for 4 hours or indicated time points at following doses: IL-17A (100 ng/ml; PeproTech), IL-17C (100 ng/ml; R&D Systems), IL-17F (1000 ng/ml; PeproTech), IL-1α (10 ng/ml; BioLegend), IL-1β (10 ng/ml; PeproTech), and TNF-α (30 ng/ml; R&D Systems). For IL-23 intracellular staining, GolgiPlug (BD Biosciences) was added to the culture system 4 hours before the test. The antibodies against mouse p-38 (Cell Signaling Technology), total p38 (Cell Signaling Technology), p-IκB (Santa Cruz Biotechnology), total IκB (Santa Cruz Biotechnology), p-Erk (Cell Signaling Technology), total Erk (Cell Signaling Technology), p-JNK (Cell Signaling Technology), and total JNK (Cell Signaling Technology) were used for Western blot analysis.

Primary human keratinocytes (neonatal human epidermal keratinocyte) were originally from Invitrogen. Cells within three passages were cultured with EpiLife medium plus EpiLife Defined Growth Supplement (EDGS) (Invitrogen), followed by the stimulation of hIL-17A (100 ng/ml; PeproTech) for 4 hours.

**Expression of His-tagged IL-17 family cytokines and binding to IL-17RD**

DNA sequence encoding His-tagged Il17a-Il17f genes were cloned into the pVRC vector. IL-17A–His to IL-17F–His expression vector was transfected into 293F cells, and the secreted His-tagged protein was purified with a nickel-charged affinity resin (Ni-NTA) (Qiagen). For the detection of binding, 293T cells were transfected with full length IL-17RD or empty vector (pcDNA3.1). Forty-eight hours after transfection, His-tagged protein was incubated with the transfected cells (37°C for 1 hour), followed by staining with phycoerythrin-conjugated anti–His mAb (37°C for 30 min). The relevant isotype control mAbs were also used. Samples were analyzed using BD Fortessa (BD Biosciences) and FlowJo software (TreeStar).

**Bimolecular fluorescence complementation**

BiFC assays were prepared according to previous studies with minor modifications (35, 36). Briefly, the sequences encoding the YFPN or YFPC were fused after the coding regions for Il17ra, Il17rc, or Il17rd to make YFPN-RA, YFPN-RC, YFPC-RA, YFPC-RC, and YFPC-RD fusion proteins. HEK293T cells were transfected with indicated combinations of plasmids for 48 hours, and the fluorescence emissions of transfected cells were assessed by flow cytometry. For cytokine-binding assays, the plasmid encoding hCD2 was cotransfected with IL-17RD plasmids using Lipofectamine 2000. Cells were harvested 48 hours after transfection and lysed with radioimmunoprecipitation assay (RIPA) buffer (pH 7.4) (CW2334S, CWBIO) containing the protease inhibitor cocktail (Thermo Fisher Scientific). Ten milligrams of total protein was used for immunoprecipitation with mouse anti-Flag antibody (clone 3C6, Easybio), and the precipitated protein complex was used for immunoblotting with antibodies against HA-tag (clone 2B11, Easybio). For HaCaT, primary mouse keratinocytes and primary human keratinocytes cells were first stimulated with or without hIL-17A or mIL-17A (100 ng/ml) for 4 hours and then lysed with RIPA buffer (pH 7.4) containing the protease inhibitor cocktail. Fifteen milligrams of total protein was used for immunoprecipitation with an anti–hIL-17RA (R&D Systems) or anti–mIL-17RA (R&D Systems), or the corresponding isotype control mAbs, and the precipitated protein complex was used for immunoblotting with antibodies against hIL-17RD or mIL-17RD (R&D Systems).

**RNA extraction and RT-qPCR**

Total RNAs were extracted by the RNAspre Pure Kit (DP431, Tiangen Biotech) from total skin samples or cultured keratinocytes, and complementary DNAs were synthesized by M-MLV (Moloney Murine Leukemia Virus) Reverse Transcriptase (Invitrogen). RT-qPCR was performed with appropriate primers and analyzed using a Bio-Rad system. The expression of target genes was normalized to the expression of housekeeping gene Actb. The primers used for RT-qPCR are listed in table S1.

**Patients with psoriasis**

Skin samples for RNA isolation and Western blot analysis were obtained from patients with psoriasis (lesional skin) or normal patients with a 2-mm punch biopsy. Sample acquisitions, including skin biopsies, were approved by the Ethics Committee of Shanghai Tenth People’s Hospital and performed in accordance with the Declaration of Helsinki Principles. Informed consent was obtained for all procedures.

**IL17RD knockdown**

Four shRNA fragments targeting human IL17RD coding sequence were designed and cloned into lentiviral vector pLKO.1-EGFP (enhanced green fluorescent protein). The pLKO.1–hIL-17RD–shRNA lentiviral plasmid and the helper plasmids were cotransfected into the 293T cells to package lentivirus, and the pLKO.1-scramble shRNA plasmid was used as negative control. The infected cells were then sorted on the basis of GFP expression. The knockdown efficiency was tested by Western blot. The cells with maximum knockdown efficiency (targeting sequence of sh#1: 5′-GCAATTACCACCCTTATT-3′) were used in subsequent studies.

**Cell sorting**

Skin cells from epidermis and dermis were prepared as described above (11) and stained with different cell surface markers (CD45+, Gr-1+, and CD11b+ for neutrophils; CD45+, CD3+, and γδ TCR for γδ T cells; CD45+, MHCII+, and langerin+ for Langerhans cells; CD45+ and CD49f+ for keratinocytes; CD11c+ and MHCII+ for DCs; and CD11b+, Ly6C+, and F4/80+ for macrophages). Neutrophils, γδ T cells, Langerhans cells, keratinocytes, DCs, and macrophages from the skin were sorted by BD FACS Aria III Cell Sorter (BD Biosciences).
Bone marrow chimera mice
The WT and KO recipient mice (Il17rd KO or Il23 KO) were first lethally irradiated (500 Rads, x2) and then reconstituted with 5 x 10^6 bone marrow cells isolated from either WT or KO donor mice. The recipient mice were subjected to IMQ-induced psoriasis-like skin inflammations 8 weeks after bone marrow reconstitution and analyzed as described above.

Enzyme-linked immunosorbent assay
Keratinocytes (5 x 10^4 cells per well) were seeded in triplicate onto 24-well plates in 0.4-ml complete 154CF medium and allowed to adhere overnight. The cells were subsequently washed and incubated with 154CF medium without supplements for 24 hours. The cells were washed again and incubated with IL-17A (100 ng/ml) for 24 hours. The concentrations of CXCL1 and CCL20 of the culture supernatants were measured using ELISA kit (Boster Biological Technology).

RNA sequencing
Keratinocyte from neonatal WT, Il17rd KO, and Il17rc KO mice were cultured and stimulated with IL-17A (100 ng/ml; PeproTech) for 8 hours. Total RNAs were isolated with the RNAprep Pure Kit (DP431), and the RNA-seq library was prepared by the Beijing Genomics Institute. Sequence reads were obtained using BGISEQ-500 (Illumina) and successfully mapped to mouse genome. Reads counts were normalized on the basis of reads per kilobase per million mapped reads (RPKM), fold changes were calculated for all possible combinations, and a twofold cutoff was used to select genes with expression changes.

Statistical analysis
The data were analyzed by Graph Prism 6.0 software, and the statistics were analyzed by unpaired Student’s t test or one-way analysis of variance (ANOVA), followed by Tukey’s post hoc test. All quantitative data are shown as means ± SEM. P values less than 0.05 were considered significant.

SUPPLEMENTARY MATERIALS
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Material and Methods
Fig. S1. Test of knockdown and knockdown efficiency in Il17rc KO mice and Il17rd knockdown human keratinocytes.
Fig. S2. IL-17RD functions as a receptor for IL-17A but not IL-17A/F in mouse keratinocytes.
Fig. S3. IL-17RC and IL-17RD are both required for the full development of IMQ-induced psoriasis-like skin inflammation.
Fig. S4. IL-17RD expression in keratinocytes is important for IMQ-induced psoriasis-like skin inflammation.
Fig. S5. Densitometry analysis of the phosphorylation of p38, lck, Erk, and JNK in primary mouse keratinocytes.
Fig. S6. The expression of psoriasis-related genes in WT, Il17rd KO, Il17rc KO, and Il17rc and Il17rd DKO keratinocytes stimulated with IL-17A.

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Interleukin-17 receptor D constitutes an alternative receptor for interleukin-17A important in psoriasis-like skin inflammation

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A new receptor for interleukin-17

The cytokines interleukin-17A (IL-17A) and IL-17F drive immune activation by binding to the IL-17 receptor (IL-17R) complex composed of two subunits, IL-17RA and IL-17RC. Here, Su et al. identify a second IL-17R complex composed of IL-17RA and IL-17RD that is expressed by skin keratinocytes. Using a mouse model of psoriasis, they report that IL-17RA/IL-17RD complex plays a vital role in driving IL-17–dependent skin inflammation. Although the IL-17RA/IL-17RC complex binds IL-17A and IL-17F homodimers and IL-17A/IL-17F heterodimers, they report here that the IL-17RA/IL-17RD specifically binds IL-17A homodimers. As antibodies targeting IL-17 cytokines and their receptors are being used in the treatment of autoimmune diseases, the discovery of a second receptor is interesting from both basic and clinical viewpoints.